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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,380	01/26/2004	Maurice M. Moloney	9369-292	4979

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EXAMINER	
RAGHU, GANAPATHIRAM	
ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/763,380	MOLONEY ET AL.	
	Examiner	Art Unit	
	GANAPATHIRAMA RAGHU	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-67* is/are pending in the application.

4a) Of the above claim(s) *51-55 and 62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-50, 56-61 and 63-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Application Status

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/19/08 has been entered.

In response to the Final-Office Action mailed on 07/01/08, applicants filed and RCE and a response with amendments on 12/19/08. Said response amended claims 42, 53, 58, 59, 60 and 61and cancelled claims 68 and 69. Claims 42-69 are pending in this application, claims 51-55 and 62 remain withdrawn as they are drawn to non-elected inventions. Claims 42-50, 56-61 and 63-67 are now under consideration.

Applicants request in their response for the rejoinder of withdrawn claims 51-55 and 62, once the independent claims are in order for allowance is noted. However, at this stage of prosecution none of the examined claims are in a condition for allowance and hence claims 51-55 and 62 remain withdrawn.

Objections and rejections not reiterated from previous action are hereby withdrawn.

Withdrawn-Claim Rejections: 35 USC § 112

Previous rejection of claim 42 (claims 43-52 and 56-59 depending therefrom), claim 60 and claim 61 (claims 62-67 depending therefrom) rejected under 35

U.S.C. 112, second paragraph is being withdrawn due to amendments to the claims and persuasive arguments.

Maintained-Claim Rejections: 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Claims 42-50, 56-61 and 63-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a chimeric nucleic acid sequence encoding a fusion polypeptide comprising the full length oil body protein oleosin (polynucleotide of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2) comprising a cleavable linker and a heterologous polypeptide (as in claims 61 and 63-67) and to a method of producing said chimeric fusion polypeptide in a host cell (as in claims 42-50 and 56-60), does not reasonably provide enablement for any chimeric nucleic acid sequence encoding a fusion polypeptide comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claim.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 42-50, 56-61 and 63-67 are so broad as to encompass any chimeric nucleic acid sequence encoding a fusion polypeptide comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of fusion-polypeptides i. e., comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell, broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and

obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to the use of a chimeric nucleic acid sequence encoding a fusion polypeptide comprising the full length oil body protein oleosin (polynucleotide of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2) comprising a cleavable linker and a heterologous polypeptide (as in claims 61 and 63-67) and to a method of producing said chimeric fusion polypeptide in a plant host cell (as in claims 42-50 and 56-60), but provides no guidance with regard to the making of variants and mutants of any oil body protein from any source linked via cleavable linker to a heterologous polypeptide and to a method of expression or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Whisstock et al., Q Rev Biophys. 2003 Aug; 36(3): 307-340), the claimed invention would require undue experimentation. Further, Li et al., (J. Biol. Chem., 2002, Vol. 277 (40): 37888-37895) teach: **i)** that there are more than 40 different oleosins, comprising a characteristic central hydrophobic domain of ~70-75 uninterrupted and uncharged residues that forms an hairpin loop around three conserved proline residues around which flanked by relatively polar C-terminal (~65 residues) and N-terminal domains (~50 residues) and these domains are diverse in

amino acid structure (Column 2, second paragraph, page 37888 and Column 2, Discussion, page 37892); **ii)** difficulty in expressing the central domain (hydrophobic domain) in *E.coli*, yeast and cell-free translation system (in fact, even the applicants' in the instant application have admitted on record that that the activity observed for fusion product is less than the unfused product when expressed in *E.coli*, Example 17: pages 62-64 of specification); **iii)** results from said study indicated that the maximum stability of reconstituted oil body emulsion is only possible with the intact oleosin protein and surface oriented amphipathic N- and C-terminal domains may play an important role in emulsion formation (column 1, second paragraph, page 37894); and **iv)** identical oleosin molecules can interact to form homo-oligomers, some of which remain associated even in the presence of strong denaturants, such as SDS. Therefore, the specification fails to teach one of ordinary skill how to make and use the full scope of the fusion polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims for any chimeric nucleic acid sequence encoding a fusion polypeptide comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell, as claimed in claims 42-50, 56-61 and 63-67, because the specification does not establish: (A) regions of the protein/polynucleotide structure which may be modified without affecting the activity of any oil body protein from any source; (B) the general tolerance of the polypeptide and the polynucleotide encoding any oil body protein from any source to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue or the respective codon in the polynucleotide with an expectation of obtaining the desired biological function with regards to any oil body protein from any source; (D) said variant fusion polypeptides adopting a molecular configuration (as amphipathic N- and C- terminal portion/domains and central hydrophobic domain are required for the stable configuration of the oil body protein, such that the cleavable site is accessible to by protease factor Xa; (E) said variant fusion polypeptides adopting a molecular configuration with desirable properties and expressed to desirable levels in a host cell and presence or absence of necessary molecular chaperones that are necessary to express and proper folding of the fusion polypeptides in a host cell and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claim broadly including methods of using polypeptides with an enormous number of modifications. The scope of the claim must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any chimeric nucleic acid sequence encoding a fusion polypeptide comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In support of their request that the prior rejection of claims 42-50, 56-61 and 63-67, under 35 U.S.C. 112, first paragraph for enablement, applicants provide the following arguments.

"Applicant has amended the independent claims in order to specify that the oil body protein comprises at least N-terminal domain and hydrophobic domain of an oil body protein… oleosins were isolated and sequenced from numerous species including without limitation…" (last paragraph of pages 9 to first paragraph of page 10 of applicants' response dated 12/19/08).

Reply: As argued by the examiner, the broadest interpretation of claims encompasses a genus of "oil body" proteins including varaints and mutants with any structure from any source and clearly constitutes undue experimentation as it would involve making and testing many parent sequences including the mutants, variants and recombinants of said parent sequences with regard to the oil body protein to be comprised in a chimeric fusion protein as the putative amino terminal and caboxy terminal regions show a great diversity among various oil body proteins (Li et al.,). This argument is also supported by the applicants' definition in pages 14-15 for an oil body protein: "oil body proteins share sequence homolgy with other oil body proteins which may be oleosins and caleosins known in the art", thus the specification is limited to teaching how to make and use fusion proteins comprising oleosins and caleosins and not any oil body protein of undefined structure from any source including variants and mutants.

Examiner would like to reiterate that examiner is not disputing the fact that the oil body proteins such as oleosins and caleosins can be used in targeting recombinant polypeptides as stated by Li et al., and has demonstrated in the instant application. Examiner's arguments are directed towards the breadth and scope of the claims as written. In addition, applicants attention is directed to Li et al., wherein it is clearly stated on page 37894, column 2, last paragraph "Our results also indicated that maximum stability of reconstituted oil body emulsions was only attained by reconstitution of the intact oleosin with oil bodies. The 9-kDa central core domain was relatively poor emulsifying and stabilizing agent. The surface-oriented N- and C-terminal domains play

an important role in emulsion formation...". In the light of this teaching by Li et al., a skilled artisan requires the structure of a parent sequence or structures having sequence homology to oleosins and caleosins, as any changes in the N- and C-terminal domain is shown to affect the stability of the oil body protein.

Written Description

Claims 42-50, 56-61 and 63-67 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 42-50, 56-60 and 63-67 are directed to any chimeric nucleic acid sequence encoding a fusion polypeptide comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell.

Claims 42-50, 56-60 and 63-67, are rejected under this section 35 U.S.C. 112, because the claims as interpreted, are directed to a genus of polynucleotides and encoding fusion polypeptides and to a method of making said fusion polypeptide that involves a genus of polynucleotides and encoding polypeptides with no support in the specification for the structural details associated with the function i.e., any chimeric nucleic acid sequence encoding a fusion polypeptide comprising any nucleic acid sequence that encodes any oil body protein of undefined structure from any source

necessary for the functional activity of said oil body protein, said fusion protein further comprising a cleavable linker and a polynucleotide encoding heterologous polypeptide and to a method of producing said chimeric fusion polypeptide in a host cell.

No description of identifying characteristics of all of the sequences of an isolated polynucleotide encoding a fusion polypeptide of any oil body protein having the associated function from any source including variants, mutants and recombinants, has been provided by the applicants in the specification. No information, beyond the characterization of an isolated chimeric nucleic acid sequence encoding a fusion polypeptide comprising the full length oil body protein oleosin (polynucleotide of SEQ ID NO: 1 encoding the polypeptide of SEQ ID NO: 2) comprising a cleavable linker and a heterologous polypeptide (as in claims 61 and 63-67) and to a method of producing said chimeric fusion polypeptide in host cell (as in claims 42-50 and 56-60) has been provided by the applicants in the specification. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed. This recitation fails to provide a sufficient description of the claimed genus of polynucleotides and encoded polypeptides as it merely describes the functional features of the genus without providing any definition of the structural features associated with the function of the species within the genus.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e.,

structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

In support of their request that the prior rejection of claims 42-50, 56-61 and 63-67, under 35 U.S.C. 112, first paragraph for written description be withdrawn, applicants' have essentially provided the following argument.

(A) "In particular, as noted previously, the structure of numerous oil body proteins were known in the art at the time the application was filed. In addition, oil body proteins from different species share structural similarity in that they comprise three domains, an N-terminal domain, a central hydrophobic domain and a C-terminal domain…Further, Applicant provided working examples showing that the two oleosins and one caleosin work in the claimed method…" (last paragraph of pages 11-12 of applicants' response dated 12/19/08).

Reply: The reply given by the examiner regarding 112, first paragraph rejection for enablement fully applies to the written description rejection also, the broadest interpretation of claims encompasses a genus of "oil body" proteins including variants and mutants with any structure and clearly constitutes undue experimentation as it

would involve making and testing many parent sequences including the mutants, variants and recombinants of said parent sequences.

The only guidance provided by the specification and art at the time of filing of the instant invention is the structural similarity of plant oleosins and caleosins and not any oil body protein from any source and even within the plant oleosins the putative amino terminal and caboxy terminal regions show a great diversity among various oil body proteins (Li et al.,). Furthermore, Li et al., also clearly state on page 37894, column 2, last paragraph "Our results also indicated that maximum stability of reconstituted oil body emulsions was only attained by reconstitution of the intact oleosin with oil bodies. The 9-kDa central core domain was relatively poor emulsifying and stabilizing agent. The surface-oriented N- and C-terminal domains play an important role in emulsion formation…". In the light of this teaching by Li et al., a skilled artisan requires the structure of a parent sequence, as any changes in the N- and C-terminal domain is shown to affect the stability of the oil body protein.

As argued above in maintaining the enablement rejection: "This argument is also supported by the applicants' definition in pages 14-15 for an oil body protein: "oil body proteins share sequence homolgy with other oil body proteins which may be oleosins and caleosins known in the art", thus the specification is limited to teaching the structure of oleosins and caleosins and not any oil body protein of undefined structure from any source including variants and mutants.

Summary of Pending Issues

The following is a summary of issues pending in the instant application.

Claims 42-50, 56-61 and 63-67 are rejected under 35 U.S.C. 112, first paragraph, for enablement and written description.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached between 8 am-4: 30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Ganapathirama Raghu/
Patent Examiner
Art Unit 1652